Samoyed Hereditary Glomerulopathy: Serial, Clinical and Laboratory (Urine, Serum Biochemistry and Hematology) Studies

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ABSTRACT

Human hereditary nephritis refers to familial glomerular diseases which may progress to renal failure. Samoyed hereditary glomerulopathy has been shown previously to be a model for hereditary nephritis. Clinical and laboratory studies were performed to follow progression to renal failure in 44 dogs in a family with Samoyed hereditary glomerulopathy. Affected males appeared healthy for their first three months but then became progressively wasted. Proteinuria was detected between two to three months of age; after five months, urine protein electrophoresis showed pre-albumin, albumin and α and β globulin peaks. From three months onward, a reduced glomerular filtration rate was detected. Serum albumin decreased while amylase, urea, creatinine and phosphate increased from four to five months of age. Death from renal failure occurred by 15 months. Carrier females also became thinner and developed proteinuria between two and three months of age, but neither renal failure nor death ensued. Hence, SHG progressed rapidly in affected males but not in carrier females.

Key words: Samoyed hereditary glomerulopathy, hereditary nephritis.

RÉSUMÉ

La néphrite humaine héréditaire désigne les maladies familiales susceptibles d'évoluer vers la défaillance rénale. On a par ailleurs déjà démontré que la glomérulopathie héréditaire du Samoyede constitue un modèle pour la néphrite humaine héréditaire. Les auteurs ont procédé à des examens cliniques et de laboratoire, pour suivre la progression de la glomérulopathie héréditaire du Samoyede, jusqu'à la défaillance rénale, chez 44 chiens d'une lignée atteinte de cette maladie. Les mâles affectés apparurent en santé, jusqu'à l'âge de trois mois; ils dépérirent ensuite graduellement. La protéinurie débuta vers l'âge de deux à trois mois; au delà de cinq mois, l'électrophorèse des protéines urinaires révéla les concentrations les plus élevées en préalbumine, albumine et globulines α et β. À compter de l'âge de trois mois, on décela une baisse du taux de filtration glomérulaire. Vers l'âge de quatre à cinq mois, l'albumine sérique diminua, tandis que l'amylase, l'urée, la créatinine et le phosphate augmentèrent. La mort, imputable à une défaillance rénale, survint vers l'âge de 15 mois. Les femelles porteuses de la tare maigrirent aussi et développèrent une protéinurie, vers l'âge de deux à trois mois, mais elles ne manifestèrent pas de défaillance rénale et ne moururent pas. Il semble donc que la glomérulopathie héréditaire du Samoyede progressa rapidement chez les mâles, mais non chez les femelles.

Mots clés: glomérulopathie héréditaire du Samoyede, néphrite héréditaire.

INTRODUCTION

Hereditary nephritis (HN) in man consists of various familial glomerular diseases, some of which may progress to renal failure (1,2). Usually it follows a more severe course in men than in women, since end-stage renal failure often develops by the end of the third decade of life in men but may never develop in women (1-3). Previously we described a family of Samoyed dogs in which affected males spontaneously developed renal failure (4). Their glomerular capillary basement membranes had extensive multilaminar splitting on examination by electron microscopy (EM) which was similar to that seen in some forms of human HN, including Alport's syndrome (4). In contrast, carrier females did not develop renal failure and examination of their glomeruli by EM showed only focal splitting (4, unpublished observations). In the present study, we have determined the rate of development of renal failure in affected male and carrier female dogs with Samoyed hereditary glomerulopathy (SHG) by performing serial clinical examinations and laboratory studies of urine, serum biochemistry and hematology.

MATERIALS AND METHODS

MAINTENANCE OF DOGS

Forty-four purebred and crossbred Samoyed dogs (31 males, 13 females) related through their dams to a line of Samoyeds affected with SHG were raised in cages and inside runs. Pups were weaned at four to six weeks of age onto moist commercial dog food

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Work supported by a grant from the Medical Research Council of Canada (MA-7603). Drs. B. Jansen and P. Thorner were fellows of the MRC.

Submitted July 30, 1986.

(Purina dog chow, containing 25% protein) and were subsequently maintained on dry commercial dog ration and water *ad libitum*. They were routinely vaccinated against distemper, adenovirus, parvovirus and rabies.

DIAGNOSIS OF RENAL DISEASE

Male dogs belonging to a pedigree with SHG were categorized as affected if examination by electron microscopy of their glomeruli showed multilaminar splitting of glomerular capillary basement membranes, the extent of which varied with age (4). In addition, as the disease progressed, protein excretion exceeded 0.3 g/L in random urine collections, there was an increase in serum creatinine which terminated in renal failure and death by 15 months of age, and examination by light microscopy of the kidneys showed a glomerulopathy which progressed to end-stage kidneys. Carrier females were identified on the basis of their giving birth to affected males. They also developed proteinuria but examination by electron microscopy of their glomeruli showed only focal areas of multilaminar splitting of glomerular capillary basement membranes, which was less extensive than that seen in affected males and did not progress over time (4). Renal biopsies were performed on all the affected male and carrier female dogs utilized in the present study.

EXAMINATION OF URINE AND RENAL FUNCTION TESTING

Urine samples were collected as free flow samples at monthly intervals, while 24 h urine collections were obtained from 12 randomly selected dogs (four affected males, two carrier females, six unaffected animals) in metabolic cages at two and four months of age. Commercial dipstick reagent strips (Ames Division, Miles Laboratories Ltd., Rexdale, Ontario) were used for routine urinalysis. In addition, the amount of protein in the urine was quantitated turbidimetrically using 20% sulfosalicylic acid. Urinary protein was also evaluated by zone electrophoresis on agarose gels in barbital buffer, pH 8.6, using an agarose film cassette electrophoresis system (Corning Medical and Scientific, Palo Alto, California). The gels were subsequently stained with an Amido Black Stain Set. A densitometer (Clifford Corning Medical and Scientific) was used to generate a scan showing the relative proportion of each urinary protein. Plasma clearance of sodium sulfanilate was employed as a measure of glomerular filtration rate (GFR) in 29 randomly selected dogs (11 affected males, 3 carrier females, 15 unaffected) (5). Clearance of sodium sulfanilate rather than inulin or creatinine was used to measure GFR to avoid repeated catheterization of the dogs and hematuria. Disappearance curves were constructed and the half-life (T1/2) for sulfanilate was calculated.

EXAMINATION OF SERUM BIOCHEMISTRY AND HEMATOLOGY

Measurements of serum urea, creatinine, amylase, inorganic phosphate, calcium, glucose, total protein, albumin, cholesterol, total and conjugated bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), and gamma glutamyl transferase (GGT) activity were performed at monthly intervals using the Parallel or KDA (both from American Monitor Corp., Downsview, Ontario) analyzers. Serum samples from 4, 11, 8, 9, 3, 5, 5, 4 and 2 affected males were analyzed at monthly intervals from one to nine months of age, while serum samples from 6, 19, 7, 7, 5, 6, 5, 7, 4, 3, 4 and 2 unaffected males were examined at monthly intervals from 1 to 12 months of age. The Coulter Plus-IV instrument (Coulter Electronics, Hialeah, Florida) was used to obtain blood cell counts, hemoglobin concentrations and erythrocyte indices.

RESULTS

CLINICAL OBSERVATIONS

Of the 44 dogs, 11 males were affected by SHG, four females were carriers and 29 dogs were unaffected. Affected males appeared healthy until three months of age, at which time they showed a decrease in growth rate and became progressively thinner than their unaffected littermates (Fig. 1). Eventually, affected males appeared emaciated. In a previous study, all affected males died from renal failure by 15 months of age (6). In the present study, all but one of the affected males were euthanized before death from uremia had occurred. Depression, vomiting, and melena were present terminally at ten months of age in the one uremic male. Carrier females also became thinner than their unaffected littermates from three months of age onward (Fig. 1) but they did not die from renal failure.

EXAMINATION OF URINE AND RENAL FUNCTION TESTING

Affected males — Proteinuria was first detected in affected males when they were between two and three months of age. The 24 h urinary protein excretion in four affected males at four months of age varied from 32 to 185 mg/kg body weight/24 h (mean ± standard deviation = 115.2 ± 63.7 mg/kg). Although urine from normal mature dogs has been reported to contain protein (13.9 ± 7.7 mg/kg/24 h) (7), none was detected in six unaffected animals in our study. The urine A/G ratio was higher in younger (≤5 months) than older affected males. Electrophoresis of normal dog urine concentrated up to 100-fold showed only a very small albumin peak. In contrast, pre-albumin, albumin, and α and β globulin peaks were seen on electrophoresis of urine concentrated to approximately 10 g/L protein in all 11 affected males, especially after five months of age (Fig. 2a). A pre-albumin peak was not seen in serum of affected males (Fig. 2b). The specific gravity of random urine samples was 1.009 ± 0.0006 (mean ± standard deviation) after five months, as measured in 30 samples obtained from seven affected males. However, ability to concentrate urine before this time was demonstrated by urine specific gravity readings of 1.025 ± 0.001 in 42 urine samples obtained from the seven affected males. In spite of normoglycemia, persistent glucosuria developed at seven to nine months in three of five affected males that survived to this age. Hemoglobinuria exceeding 1+ on a dipstick test and/or microscopic hematuria (>10 RBC/high power field), unrelated to catherization or the trauma of renal biopsy, was seen more often in affected males (61% of urinalyses) than in carrier females or unaffected dogs (21% of urinalyses). Plasma

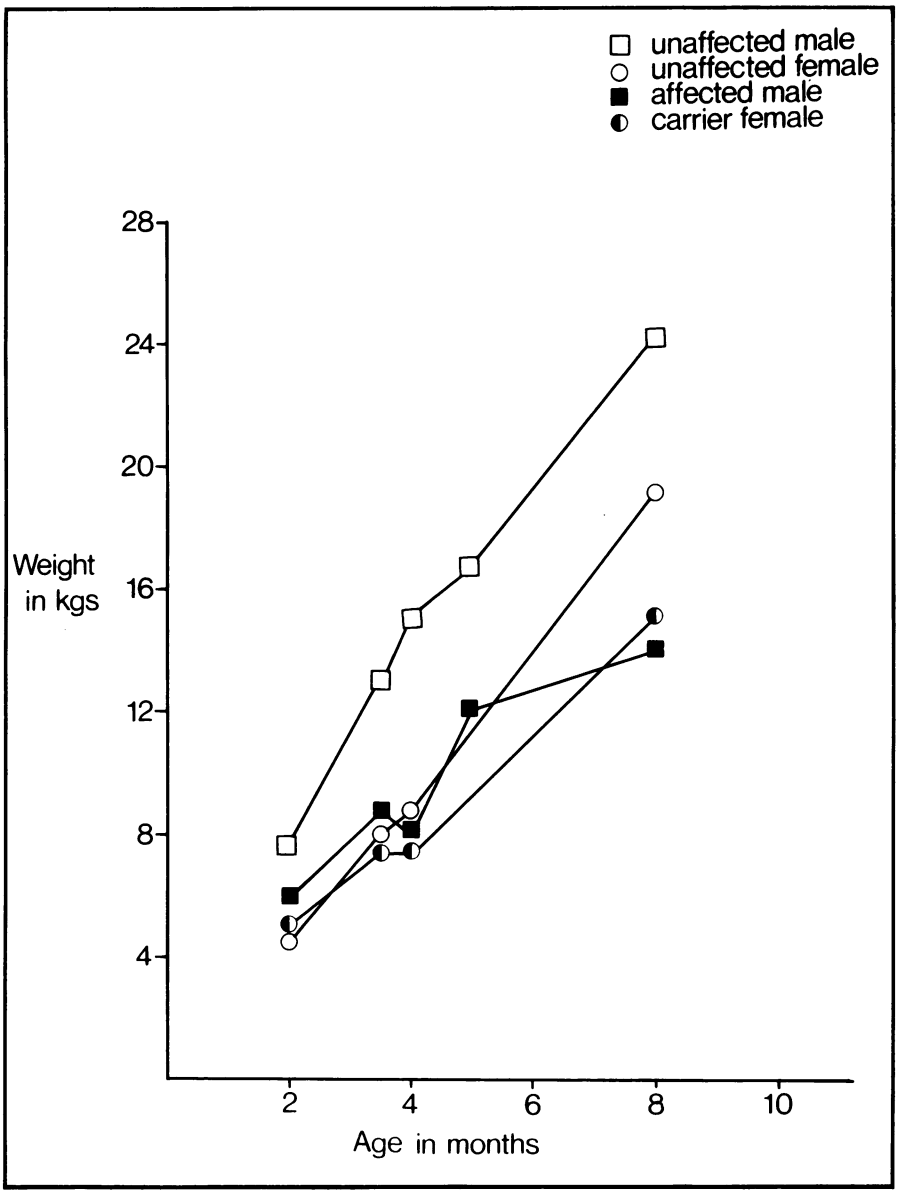

Fig. 1. Weights of affected male and carrier female dogs with Samoyed hereditary glomerulopathy and unaffected male and female Samoyed dogs. Four dogs from a single litter were weighed at the times indicated.

T1/2 of sodium sulfanilate was normal in affected males at two months but was increased at three, six and eight months of age, indicating a reduced GFR (Table I).

Carrier females — Proteinuria was first seen in the four carrier females at the same age as in affected males (i.e. two to three months). Twenty-four hour protein excretion was 204 mg/kg body weight at four months of age in one carrier female and 35.3 mg/kg at 19 months in one other. The urine A/G ratio was similar in young and mature carrier female dogs. Albumin and α and β globulin peaks were seen on urine electrophoresis in three of three carrier females (Fig. 2c) but a prealbumin peak was seen in only one of these females at ten months of age. No other urinary abnormalities were noted. Plasma T1/2 of sodium sulfanilate was normal in one carrier female at six, and two carrier females at eight months of age, indicating a normal GFR.

TABLE I. T1/2 for Plasma Clearance of Sodium Sulfanilate in Unaffected Dogs, Affected Male Dogs with Samoyed Hereditary Glomerulopathy and Carrier Females

Age (Months)	Unaffected No. of Dogs	T1/2	Affected Males No. of Dogs	T1/2	Carrier Females No. of Dogs	T1/2
2	2	46 ± 1	2	46 ± 1		
3	1	45	2	80 ± 4		
6	3	69 ± 8	4	155 ± 8	1	76
8	9	70 ± 12	3	175 ± 6	2	68 ± 11

The values shown in the table for T1/2 are mean minutes ± standard deviations

BIOCHEMICAL EXAMINATION OF SERUM

Affected males — Hypoalbuminemia developed at three to four months of age and serum albumin remained below 20 g/L after four months (Fig. 3A). Cholesterol did not differ from normal, except at nine months, when hypercholesterolemia was seen occasionally. Serum amylase activity increased progressively from five to eight months, when a decrease was seen in the two affected males surviving beyond this time (Fig. 3B). Serum urea and creatinine (Fig. 3C) became elevated at five months and continued to increase until euthanasia. Normally, young growing dogs have elevated serum inorganic phosphate and alkaline phosphatase levels (8). However, serum inorganic phosphate remained elevated in affected males and increased progressively after six months of age, in contrast to a gradual fall to the normal adult range by ten months of age in unaffected males (Fig. 3D). Serum calcium values varied but tended to be at the higher limit of normal. No abnormalities were seen in serum levels of AST, GGT, ALT, glucose, bilirubin, or CK.

Carrier females — Occasionally carrier females developed mild, transient hypoalbuminemia but no biochemical changes indicative of renal failure were seen, even up to 30 months of age.

EXAMINATION OF BLOOD

No hematological abnormalities were identified in affected males or carrier females, except for a mild, normocytic anemia in two of the two month old affected males, which resolved without treatment, and in one azotemic affected male at eight months of age.

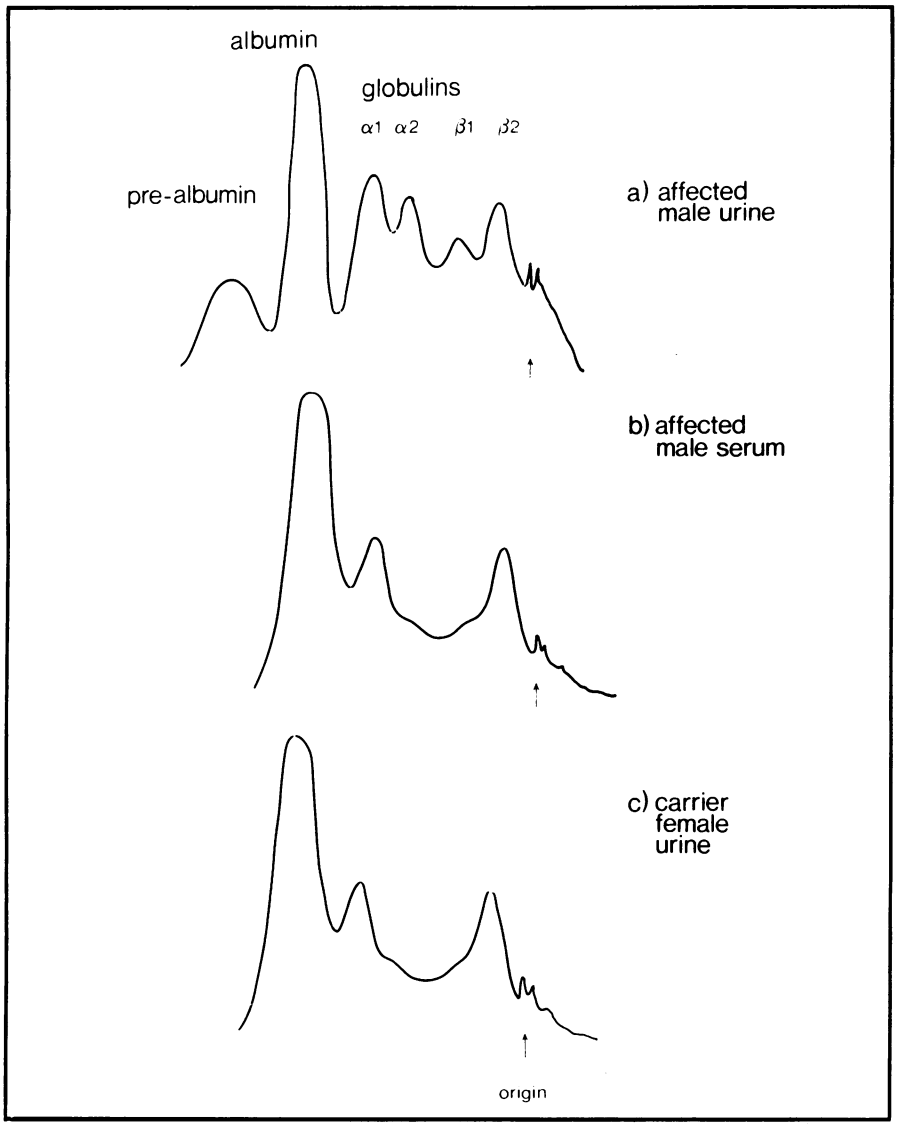

Fig. 2. Serum and urine protein electrophoresis of affected male with Samoyed hereditary glomerulopathy (SHG) and carrier female dog. a) Urine protein electrophoresis of affected male with SHG. b) Serum protein electrophoresis of affected male with SHG. c) Urine protein electrophoresis of carrier female.

DISCUSSION

Many forms of renal disease, often progressing to renal failure, have been described in dogs, including Samoyed (4,9), Doberman pinschers (10,11), cocker spaniels (12,17), Norwegian elkhounds (17,18), Lhasa apsos, shih-tzus (19), soft-coated wheaten terriers (21,22), bull terriers (23), malamutes (24), and keeshonds (25). Proteinuria has been found consistently in Samoyeds (9), Doberman pinschers (10) and cocker spaniels (12,15) but not in Norwegian elkhounds (17), Lhasa apsos, shih-tzus (19) or wheaten terriers (21). In contrast to all other breeds, only Samoyeds have shown more rapid progression to renal failure in males and less severe renal disease in females (9). However, further work is required to characterize these renal diseases in dogs since there is a paucity of ultrastructural studies and few instances of early renal disease have been described. Although it is possible that other breeds will be shown to have renal disease similar to that in Samoyeds, the morphological changes seen in the kidneys of Samoyeds closely resemble those in human HN (4). Hence we have utilized SHG as a model for human HN.

The clinical course of SHG was extremely rapid in affected male dogs. They appeared healthy during their first three months of life but then suffered a decrease in growth rate (Fig. 1), became progressively thinner and wasted, and died by 15 months of age. These clinical changes were accompanied by the development of persistent proteinuria at two to three months of age, followed by azotemia after five months and renal failure after seven months. Proteinuria also developed in carrier female dogs at two to three months of age but renal failure did not follow. The only change noted in their appearance as they became older was failure to achieve normal weight (Fig. 1). The difference in severity of the clinical course of SHG in male versus female dogs was reminiscent of that seen in human HN, where affected men usually progress rapidly to renal failure while women often live a normal lifespan (1,2).

One report has documented biochemical abnormalities indicative of renal failure in a carrier female dog with SHG and historical data suggest that renal failure was the cause of death in one carrier female in the family of Samoyeds that we are studying (9). However, it is possible that sporadic renal disease, commonly seen in older dogs, may have occurred in these two carrier females, or that carrier females show variability of expression of SHG as do women with HN. However, the carrier females described in the present study, including two that are now four years old, did not develop clinical or biochemical evidence of renal failure.

Various abnormalities seen in the urine of both affected male and carrier female dogs deserve comment. *First*, proteinuria was the initial indication of SHG and hematuria was not a consistent feature, although it occurred more often in affected males than in carrier female or unaffected dogs. In contrast, in human HN, hematuria is usually the initial feature of renal disease (1,2,26,27) and proteinuria is not invariably present at onset. *Second*, proteinuria in affected male dogs was moderately selective before five months of age, as shown by the high A/G ratio, but then became nonselective, with an increased amount of globulin in the urine, consistent with the development of a more severe lesion of glomerular capillary basement membranes (28). In contrast, proteinuria remained selective in carrier female dogs. *Third*, a pre-albumin peak, which was not present in serum, was identified on electrophoresis of urine obtained from all affected male

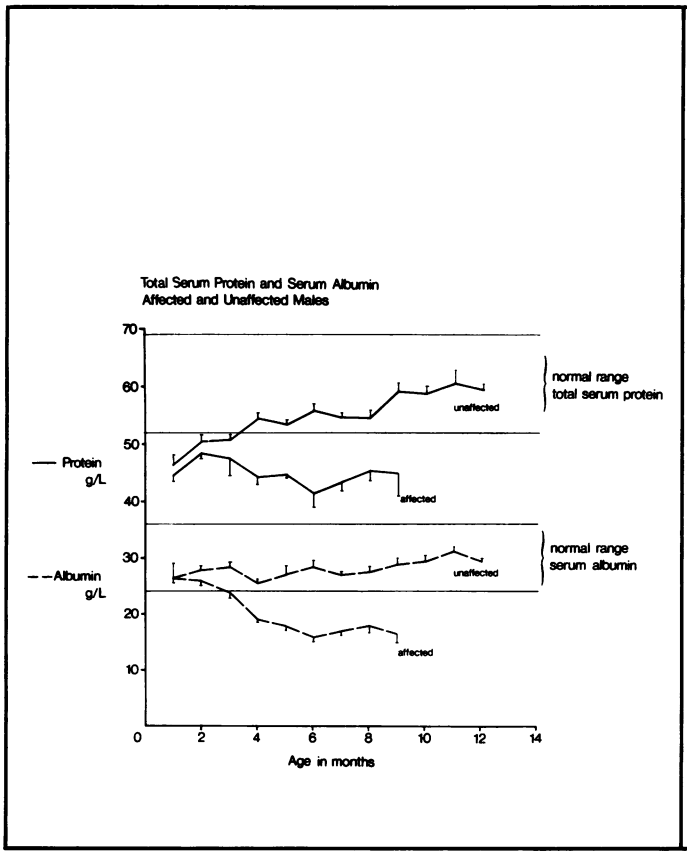

Fig. 3A. Total serum protein and serum albumin.

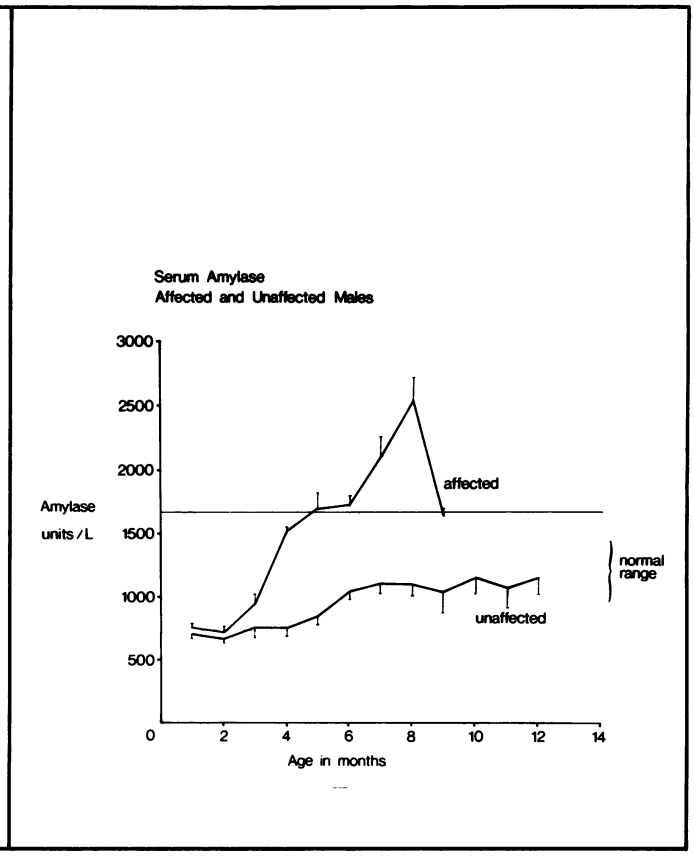

Fig. 3B. Serum amylase.

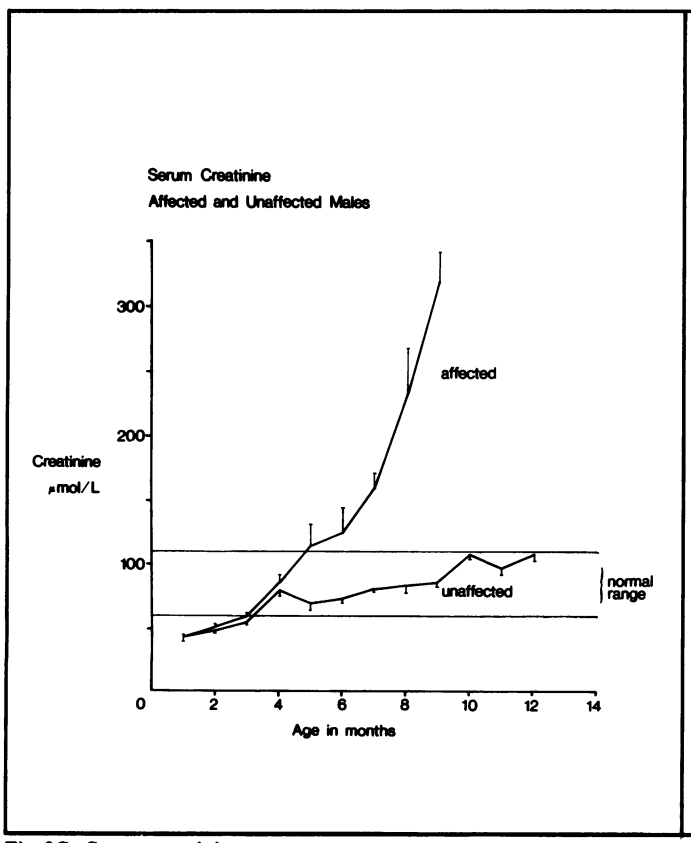

Fig. 3C. Serum creatinine.

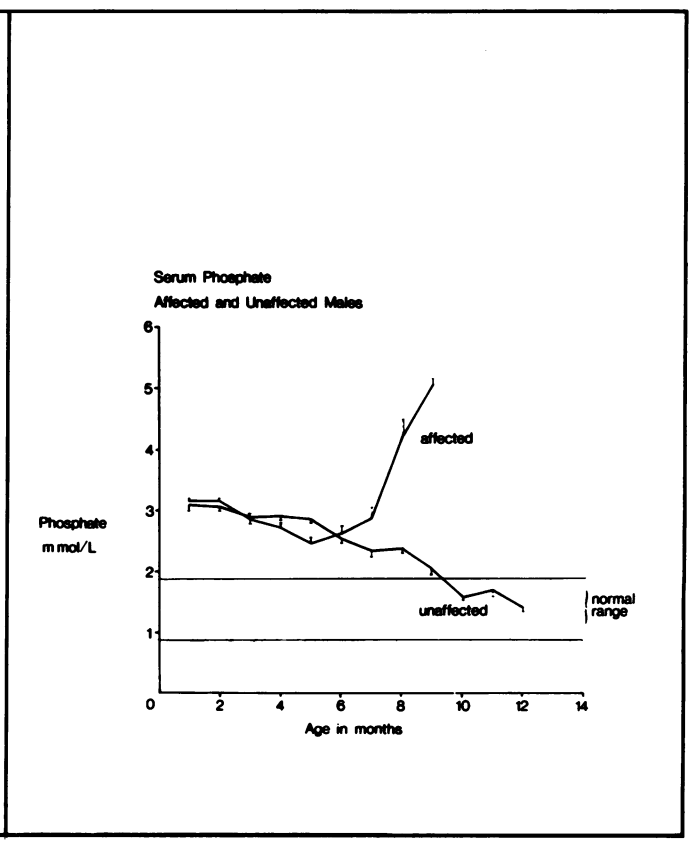

Fig. 3D. Serum inorganic phosphate.

Fig. 3. Determination of serum biochemistry in affected male dogs with Samoyed hereditary glomerulopathy and unaffected dogs. The values shown are means ± standard errors of determinations performed on serum of affected and unaffected males.

dogs but was seen only in the urine of some carrier females. The protein may have been derived from albumin or some other plasma protein which was electrophoretically altered in its passage through the glomerulus, or it may have originated from the kidney itself. The presence of this protein in the urine of affected male but only occasionally in carrier female dogs may have been a reflection of the difference between the sexes in the severity of the lesion of glomerular capillary basement membranes. Urine pre-albumin was reported to be present in one study of proteinuric dogs (29) but has not been described in human HN. Urine protein electrophoresis of patients with Alport's syndrome has also shown a component in the α 1 region (30), which was found to be the complement breakdown product C3b (31). *Fourth*, glucosuria in affected males in the later stage of SHG, in the face of normal serum glucose levels, indicated the development of an abnormality in tubular reabsorption of filtered glucose. *Fifth*, the low specific gravity of the urine of 1.009 ± 0.006 seen after five months of age in affected male dogs indicated that the ability of the kidneys to concentrate the urine was impaired, presumably because of severe renal damage. Carrier female dogs did not develop glucosuria or a low specific gravity of urine.

A progressive fall in sodium sulfanilate clearance from plasma to urine in affected male dogs, beginning at three months of age, indicated progression from a normal to a reduced GFR. The reduced GFR occurred at about the same time as the onset of multilaminar splitting of glomerular capillary basement membranes (unpublished observations) and proteinuria, but before the onset of azotemia. The progressive increases in serum amylase activity, urea, creatinine, and inorganic phosphate, compounds normally filtered by the glomerulus, were nonspecific indicators of a reduction in GFR and the development of chronic renal failure. These abnormalities, which were not seen in carrier females, were not pathognomonic of SHG. In addition to the foregoing changes in serum biochemistry which reflected impaired renal function, hypoalbuminemia indicated that renal protein loss exceeded the protein synthesizing capacity of the liver. Finally, hypercholesterolemia was found in only some of the affected male dogs. These latter abnormalities, in association with proteinuria and edema, are hallmarks of the nephrotic syndrome, a frequent finding during the course of human HN (2,27). However, edema is not commonly observed in dogs, unless the serum albumin falls below 10 g/L (32).

In conclusion, SHG progressed rapidly to renal failure and death in affected male dogs and in this way resembled the early renal failure seen in affected men with HN. In contrast, renal failure and death were not seen in carrier female dogs, as is the case in many women with HN.

ACKNOWLEDGMENTS

We thank the staff in the Animal Holding Unit and the Clinical Pathology Laboratory at the Ontario Veterinary College for their assistance with this project. Money for some of the equipment purchased for this study was provided by the Natural Sciences and Engineering Research Council (NSERC) and the Ontario Ministry of Colleges and Universities. This paper was prepared with the assistance of the Medical Publications Department, The Hospital for Sick Children, Toronto.

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